IN THE CLAIMS

1 - 4 (CANCELLED)

5. (PREVIOUSLY PRESENTED) A method for indicating viability of transplanted progenitor or stem cells grown in a culture, the method being performed with a medical device that supports at least one sensing function, the method comprising:

non-destructively observing a region of a patient to where progenitor or stem cells grown in a culture cells have been transplanted;

sensing a property within said region of a patient that is indicative of cell viability or inviability of transplanted progenitor or stem cells grown in a culture; and

using data from sensing said property within said region to indicate cell viability from a transplant of progenitor or stem cells grown in a culture within the region wherein said cell viability is indicated by a property in cell chemistry resulting from an event selected from the group consisting of cell activity, cell inactivity, cell growth, cell death, specific cell function, specific cell dysfunction, volumetric expansion of cell population, and volumetric decrease of cell population.

6. (PREVIOUSLY PRESENTED) A method for indicating viability of transplanted progenitor or stem cells grown in a culture, the method being performed with a medical device that supports at least one sensing function, the method comprising:

non-destructively observing a region of a patient to where progenitor or stem cells grown in a culture cells have been transplanted;

sensing a property within said region of a patient that is indicative of cell viability or inviability of transplanted progenitor or stem cells grown in a culture; and

using data from sensing said property within said region to indicate cell viability from a transplant of progenitor or stem cells grown in a culture within the region, wherein said non-destructively observing comprises magnetic resonance imaging and wherein said cell viability is indicated by a property in cell chemistry resulting from an event selected from

the group consisting of cell activity, cell inactivity, cell growth, cell death, specific cell function, specific cell dysfunction, volumetric expansion of cell population, and volumetric decrease of cell population.

7. (PREVIOUSLY PRESENTED) A method for indicating viability of transplanted progenitor or stem cells grown in a culture, the method being performed with a medical device that supports at least one sensing function, the method comprising:

non-destructively observing a region of a patient to where progenitor or stem cells grown in a culture cells have been transplanted;

sensing a property within said region of a patient that is indicative of cell viability or nonviability of transplanted progenitor or stem cells grown in a culture; and using data from sensing said property within said region to indicate cell viability from a transplant of progenitor or stem cells grown in a culture within the region wherein said property is monitored by observation of at least one parameter selected from the group consisting of local lactate levels, local glucose turnover, local phosphorous high-energy metabolite concentrations, local F-19 labeled metabolites, alterations in tissue sodium, and changes in the conversion rates of O_2 gas to H_2O water.

8. CANCELLED

9. (PREVIOUSLY PRESENTED) The method of claim 6 wherein said property is monitored by observation of at least one parameter selected from the group consisting of local lactate levels, local glucose turnover, local phosphorous high-energy metabolite concentrations, local F-19 labeled metabolites, alterations in tissue sodium, and changes in the conversion rates of O_2 gas to H_2O water.

10. CANCELLED

11. (PREVIOUSLY PRESENTED) The method of claim 5 wherein said property is monitored by at least one technique selected from the group consisting of proton spectroscopy, monitoring of C-13 labeled glucose, monitoring by P-31 MR spectroscopy, monitoring of local F-19 labeled metabolites, monitoring of Na-23 levels, and monitoring of $17O_2$ gas conversion to H_217O water.

12. (ORIGINAL) The method of claim 6 wherein said property is monitored by at least one technique selected from the group consisting of proton spectroscopy, monitoring of C-13 labeled glucose, monitoring by P-31 MR spectroscopy, monitoring of local F-19 labeled metabolites, monitoring of Na-23 levels, and monitoring of $17O_2$ gas conversion to H_217O water.

13. (PREVIOUSLY PRESENTED) The method of claim 5 wherein said medical device includes at least one element selected from the group consisting of a volume coil surrounding the tissue and a local multi-tuned MRI RF coil.

14. (PREVIOUSLY PRESENTED) The method of claim 6 wherein said medical device includes at least one element selected from the group consisting of a volume coil surrounding the tissue and a local multi-tuned MRI RF coil.

15. (ORIGINAL) The method of claim 9 wherein said medical device includes at least one element selected from the group consisting of a volume coil surrounding the tissue and a local multi-tuned MRI RF coil.

16. (ORIGINAL) The method of claim 12 wherein said medical device includes at least one element selected from the group consisting of a volume coil surrounding the tissue

and a local multi-tuned MRI RF coil.

17. (PREVIOUSLY PRESENTED) A method for indicating viability of transplanted progenitor or stem cells grown in a culture, the method being performed with a medical device that supports at least one sensing function, the method comprising:

non-destructively observing a region of a patient to where progenitor or stem cells grown in a culture cells have been transplanted;

sensing a property within said region of a patient that is indicative of cell viability or inviability of transplanted progenitor or stem cells grown in a culture; and using data from sensing said property within said region to indicate cell viability from a transplant of progenitor or stem cells grown in a culture within the region wherein said property comprises blood flow or changes in blood flow as vascular supply is developed.

18. (PREVIOUSLY PRESENTED) The method of claim 17 wherein said non-destructively observing comprises magnetic resonance imaging and said property comprises blood flow or changes in blood flow as vascular supply is developed.

19. (PREVIOUSLY PRESENTED) The method of claim 17 wherein said property is monitored by observation of at least one parameter selected from the group consisting of local lactate levels, local glucose turnover, local phosphorous high-energy metabolite concentrations, local F-19 labeled metabolites, alterations in tissue sodium, and changes in the conversion rates of O_2 gas to H_2O water said property comprises blood flow or changes in blood flow as vascular supply is developed.

20. (ORIGINAL) The method of claim 17 wherein blood flow or changes in blood flow are measured by observation of at least one material selected from the group consisting of labeled H_2O water, contrast-agent infusion of TI-shortening agents or T2*-shortening

agents, local introduction of hyperpolarized Xenon gas, or optically-active coloring agents.

21. (ORIGINAL) The method of claim 18 wherein blood flow or changes in blood flow are measured by observation of at least one material selected from the group consisting of labeled H_2O water, contrast-agent infusion of TI-shortening agents or T2*-shortening agents, local introduction of hyperpolarized Xenon gas, or optically-active coloring agents.

22. (ORIGINAL) The method of claim 19 wherein blood flow or changes in blood flow are measured by observation of at least one material selected from the group consisting of labeled H_2O water, contrast-agent infusion of TI-shortening agents or T2*-shortening agents, local introduction of hyperpolarized Xenon gas, or optically-active coloring agents.

23. (PREVIOUSLY PRESENTED) A method for indicating viability of transplanted progenitor or stem cells grown in a culture, the method being performed with a medical device that supports at least one sensing function, the method comprising:

non-destructively observing a region of a patient to where progenitor or stem cells grown in a culture cells have been transplanted;

sensing a property within said region of a patient that is indicative of cell viability or inviability of transplanted progenitor or stem cells grown in a culture; and

using data from sensing said property within said region to indicate cell viability from a transplant of progenitor or stem cells grown in a culture within the region wherein said non-destructively observing comprises magnetic resonance imaging and said property comprises anisotropic water diffusion.

24. (PREVIOUSLY PRESENTED) The method of claim 5 wherein said property comprises the local concentrations of at least one of choline, NAA, GABA, phosphocholine, and creatine.

25. (PREVIOUSLY PRESENTED) The method of claim 6 wherein the property is selected from the group consisting of a) local tissue density and cell populations, b) local electrical activity, c) local oxygenated/deoxygenated hemoglobin and changes in the local T2* reflecting the alterations in tissue oxygenation, d) changes in the vascular reserve and response to oxygenation stresses, e) tissue fluorescence and bioluminescence, f) tissue fluorescence and bioluminescence, g) electrical impedance, and h) local tissue temperature.

26. (PREVIOUSLY PRESENTED) The method of claim 5 wherein the property is selected from the group consisting of a) local tissue density and cell populations, b) local electrical activity, c) local oxygenated/deoxygenated hemoglobin and changes in the local T2* reflecting the alterations in tissue oxygenation, d) changes in the vascular reserve and response to oxygenation stresses, e) tissue fluorescence and bioluminescence, f) tissue fluorescence and bioluminescence, g) electrical impedance, and h) local tissue temperature.

27. (CANCELLED)

28. (CANCELLED)

29. (PREVIOUSLY PRESENTED) A method for indicating viability of transplanted progenitor or stem cells grown in a culture, said method being performed with a medical device that supports at least one sensing function comprising:

non-destructively observing a region of a patient to where progenitor or stem cells

grown in a culture have been transplanted;

sensing a property within said region of a patient that is indicative of cell metabolism;

repeating or continuing said sensing of a property over a period of time in which said property changes; and

using data from sensing changes in said property within said region to indicate cell viability from a transplant of progenitor or stem cells grown in a culture within the region, wherein said data from sensing changes in said property indicates active metabolic function in transplanted cells, and wherein changes in said property are monitored by at least one technique selected from the group consisting of proton spectroscopy, monitoring of C-13 labeled glucose, monitoring by P-31 MR spectroscopy, monitoring of local F-19 labeled metabolites, monitoring of Na-23 levels, and monitoring of $17O_2$ gas conversion to H_217O water.

30 - 53 (CANCELLED)

54. (PREVIOUSLY PRESENTED) The method of claim 5 wherein the sensing of a property within said region of a patient that is indicative of cell viability or inviability of the implanted colony of cells is used to quantitate the cell viability.

55. (PREVIOUSLY PRESENTED) The method of claim 6 wherein the sensing of a property within said region of a patient that is indicative of cell viability or inviability of the implanted colony of cells is used to quantitate the cell viability.

56. (PREVIOUSLY PRESENTED) The method of claim 7 wherein the sensing of a property within said region of a patient that is indicative of cell viability or inviability of the implanted colony of cells is used to quantitate the cell viability.

57. (PREVIOUSLY PRESENTED) The method of claim 17 wherein the sensing of a property within said region of a patient that is indicative of cell viability or inviability of the implanted colony of cells is used to quantitate the cell viability.

58. (PREVIOUSLY PRESENTED) The method of claim 19 wherein the sensing of a property within said region of a patient that is indicative of cell viability or inviability of the implanted colony of cells is used to quantitate the cell viability.

59. (PREVIOUSLY PRESENTED) A method for indicating viability of transplanted progenitor or stem cells, the method being performed with a medical device that supports at least one sensing function, the method comprising:

non-destructively observing a region of a patient to where progenitor or stem cells have been transplanted;

sensing a property within said region of a patient that is indicative of cell viability or inviability of transplanted progenitor or stem cells; and

using data from sensing said property within said region to indicate cell viability from a transplant of progenitor or stem cells within the region wherein said cell viability is indicated by a property in cell chemistry resulting from an event selected from the group consisting of cell activity, cell inactivity, cell growth, cell death, specific cell function, specific cell dysfunction, volumetric expansion of cell population, and volumetric decrease of cell population.

STATUS OF CLAIMS

Claims 5-7, 9, 11-26, 29 and 54-64 are all of the claims remaining in this application, all other claims having been voluntarily cancelled during prosecution of this application, Applicants reserving the rights to file continuation application son the subject matter of those cancelled claims and other subject disclosed but not claimed in this Application.

Claims 5, 6, 13, 14, 17, 18, 20, 21, 25, 26, 54, 55, 57 and 58 have been rejected under 35 USC 102(b) as anticipated by US Patent No. 5,869,463 (Major).

Claims 7, 9, 11, 15, 16, 19, 22, 29, 56 and 58 have been rejected under 35 USC 103(a) as unpatenable over Major (as applied against claim 5) when further considered with US Patent No. 5,497,770 (Morcos).

Claims 24 has been rejected under 35 USC 193(a) as unpatentable over Major et al. in view of Chenevert (US Patent No. 6,567,684).

Claims 24 has been rejected under 35 USC 193(a) as unpatentable over Major et al. in view of Dinsmore.

ARGUMENT AGAINST REJECTIONS

FUNDAMENTAL LACK OF RECOGNITION OF LIMITATIONS IN THE CLAIMS

Each of the rejections fails to recognize specific limitations in the claims and fails to recognize the complete lack of teaching of those specific limitations in the art of record.

To summarize, the claims require the **SENSING OF A PROPERTY** in the region of a patient under examination, and the **use of that sensed property** to provide information **RELATING TO CELL CHEMISTRY** that is **INDICATIVE OF CELL ACTIVITY OR INACTIVITY**. These steps are consistently and completely absent from the combination of references used in the rejection.

The references tend to show direct visual observation of cells and determining directly from visualization whether or not the cells are there. That step and format is not within the scope of the claims, so the present claims are novel, and there is no teaching of the indirect measurement of properties that reflect cell activity or inactivity to determine cell viability or non-viability (cells are dead, dying, or non-functioning). The fundamental process steps of the present technology are not disclosed in any individual reference or the combination of references as explained in greater detail below.

The Comments of the Examiner in Response to Previous Arguments

In the Office Action, the Examiner has restated the original rejection and responds to issues raised by the Applicants as follows:

1) "Major et al. teach...various properties are evaluated such as graft rejection, inflammation response, and tumor formation of the transplanted cells in a post-transplantation (col. 4 lines 7-15)."

This citation is merely a description of purported final results of the transplantation, **not a determination of those properties by an imaging method as described in the claims.** The invention of Major et al. is the actual transplantation of cells (e.g., column 3, lines 28-43), not the observation of those cells under special circumstances to determine visual properties **INDICATED** by visual changes caused by changes in a property in cell chemistry that ""...an event selected from the group consisting of cell activity, cell inactivity, cell growth, cell death, specific cell function, specific cell dysfunction, volumetric expansion of cell population, and volumetric decrease of cell population" has occurred. The claims require sensing of data obtained *in vivo* and analysis of that data without *in vitro* removal to indicate the changes in the cell chemistry have occurred, thereby indicating the appropriate change in cell viability or condition.

As noted in detail in the arguments below, the cells in Major are examined *in vitro* before implantation to determine the quality status of the cells and then implanted. There is no disclosure of the process recited in the claims. The mere fact that the rejection points out a disclosure in Major that his implantation procedure (with prior *in vitro* examination of cells) is not surprising, nor is indicative that Major performs a process as recited by Applicants as an *in vivo* non-invasive observation examination which **IS NOT DISCLOSED by Major.** The issue raised by the Patent and Trademark Office to refute the arguments of Applicant is clearly in error.

Major specifically states:

> "**Prior to implantation**, the viability of the cells may be assessed as described by Brundin et al., Brain Res., 331:251-259 (1985), incorporated herein by reference. Briefly, sample aliquots of the cell suspension (1-4μl) are mixed on a glass slide with 10 .mu.l of a mixture of acridine orange and ethidium bromide (3.4 μg/ml of each component in 0.9% saline; Sigma). The suspension is transferred to a hemocytometer, and viable and non-viable cells were visually counted using a fluorescence microscope under epi-illumination at 390 nm. combined with white light trans-illumination to visualize the counting chamber grid. Acridine orange stains live nuclei green, whereas ethidium bromide will enter dead cells resulting

> in orange-red fluorescence. Cell suspensions should generally contain more than about 98% viable cells." (Column 7, lines 42-56, **emphasis** added)

The only type of post-implantation observation of implanted cells referred to by Major is the direct visual comparison of cells in FIG. 3 as described in column 11, lines 17-25. This is not a determination of cell chemistry, but merely a casual view of the cells to show that at a specific time, those cells are physically there. This is not a step recited within the claims, which require determination of cell chemistry indicative of changes in cell status.

The one-month observation time here to evidence cell viability is direct observation of the cells themselves by MRI, not an analysis of changes in cell chemistry by measurement of properties in the cell region indicative of cell changes. **Direct observation by MRI (or any other non-invasive or invasive) and comparison of cells themselves is not a step within the scope of the present claims.**

The present claims are **NOT** generic to any post-implantation process for determination of cell viability. The claims are specifically limited to processes that perform the steps of:

> "...**sensing a property within said region of a patient that is indicative of cell viabiliy or inviability of transplanted progenitor or stem cells** grown in a culture; and
>
> using data from sensing said property within said region to indicate cell viability from a transplant of progenitor or stem cells grown in a culture within the region wherein said cell viability is indicated by a property in cell chemistry resulting from an event selected from the group consisting of cell activity, cell inactivity, cell growth, cell death, specific cell function, specific cell dysfunction, volumetric expansion of cell population, and volumetric decrease of cell population."

Nothing in the present recitation of claims includes mere direct visual observation and reading of images of cells and estimating viability by looking directly at cells, **without**

any determination of properties indicative of cell properties. The teachings of Major do not show that step and the steps of:

> "...**using data from sensing said property** within said region **to indicate cell viability...wherein said cell viability is indicated by a property in cell chemistry**."

These are definitive and positive steps recited in this claim that are not taught by Major. The rejection is absolutely and clearly in error.

If the Patent and Trademark Office wishes to persist in this rejection, it is courteously requested to point out what specific disclosure in the specification of Major demonstrates an *in vivo* examination of local cell chemistry as the basis for observational determination that there is cell survival *in vivo*, and that the recited state of the cells is determined by the analysis.

Claims 5, 6, 13, 14, 17, 18, 20, 21, 25, 26, 54, 55, 57 and 58 have been rejected under 35 USC 102(b) as anticipated by US Patent No. 5,869,463 (Major).

Claim 5 will first be discussed to emphasize specific limitations (not to the exclusion of other limitations or claim) that are particularly material to differentiation from this combination of references. Claim 5 recites:

> A **method for indicating viability of transplanted progenitor or stem cells** grown in a culture, the method being performed with a medical device that supports at least one sensing function, the method comprising:
>
> non-destructively observing a region of a patient to where progenitor or stem cells grown in a culture cells have been transplanted;
>
> **sensing a property within said region of a patient that is indicative of cell viability or nonviability of transplanted progenitor or stem cells** grown in a culture; and
>
> **using data from sensing said property** within said region **to indicate cell**

viability from a transplant of progenitor or stem cells grown in a culture within the region **wherein said cell viability is indicated by a property in cell chemistry resulting from an event selected from the group consisting of cell activity, cell inactivity, cell growth, cell death, specific cell function, specific cell dysfunction, volumetric expansion of cell population, and volumetric decrease of cell population.** (Emphasis added).

Errors by the Examiner Regarding the Factual Content of the Major et al. reference

These argument are also applicable to arguments against previous claims where similar limitations have appeared and are argued against rejection over Major.

It is asserted that Major et al. disclose a method for indicating viability of transplanted progenitor or stem cells grown in a culture (The Examiner citing col. 5, lines 31-67, col. 6, lines 1-16, col. 7, lines 33-41) which involves sensing a property indicative of cell viability using a medical device (col. 11, lines 28-36). This assertion does not reflect the actual content of the Major et al. disclosure. Unlike the present application, Major et al. do not disclose the use of a medical device that supports sensing the viability of the cells while the cells are implanted in a human.

Major et al. actually describe the use of a number of *in vitro* (**not** ***in vivo***) methods to develop viable implantable cells. Monitoring of cell viability is performed before the cells are actually transplanted into human tissue and a patient is examined after implantation for only tumor formation. Claim 1 of Major, for example, discloses a method:

> "...comprising implanting into said mammal a therapeutically effective amount of a nontumorigenic and non-inflammatory immortalized human neuro-glial cell line..."

Figs. 1-2 of Major et al. similarly describe ex vivo preparation of implantable cells before they are implanted into tissue. Both Claim 1 and Figs. 1-2 of Major et al. disclose methods for monitoring cell viability before any transplant of the cells into a human. Figs. 3-8 and Fig.10 describe methods for post-mortem analysis of cell viability (histological examination of cell implants). Fig. 9 describes the use of MRI to evaluate the transplanted cells at a single time point 6 months after implantation, but only for tumor formation, not for cell viability.

None of the examples cited in Major et al disclose in vivo methods for monitoring or sensing cell viability following transplant of the cells into a human.

Examples 1, 6 & 7 describe in vitro methods for preparing the cells for implantation.

Example 2 describes surgical methods for implanting the cells, but not for monitoring cell viability in vivo.

Example 3 describes how "successful engraftment" of the cells was monitored by post-mortem histological methods, not by the recited steps of Claim 5:

> "...sensing a property within said region of a patient that is indicative of cell viability or inviability of transplanted progenitor or stem cells grown in a culture; and using data from sensing said property within said region to indicate cell viability from a transplant of progenitor or stem cells grown in a culture within the region wherein said cell viability is indicated by a property in cell chemistry resulting from an event selected from the group consisting of cell activity, cell inactivity, cell growth, cell death, specific cell function, specific cell dysfunction, volumetric expansion of cell population, and volumetric decrease of cell population."

Example 4 describes how MRI was used 1 month following cell implant, but only tumor formation, not cell viability, was evaluated.

Example 5 describes only post mortem histological methods to evaluate the cell implant, which also is no sensing a property within a region of a patient indicative of cell

viability. By its very nature, post mortem analysis cannot be within a region of a patient as there is no longer a patient, but a cadaver.

Thus, there is no teaching in Major et al. (as has been asserted) for using a medical device for *in vivo* monitoring of the viability of implanted cells. Although Major et al. describe the use of MRI to **initially position the cells at target locations in human tissues**, they do not provide any *in vivo* imaging method that enables the longitudinal monitoring of the survival of implanted cells over time. Major et al. simply state that

"Persons of skill will understand how to determine proper cell dosages."

This is no more than a pretreatment or concurrent treatment consideration of initial dosage application of cells. It in no way senses cell viability. Additionally, this statement ignores recent published studies that poor implant survival is a key limitation to establishing transplant efficacy. Recent reports indicate that 80-95% of embryonic stem cells die within 48 hours after implantation. Moreover, surviving implanted cells may re-innervate only 25% of the host brain tissue and only at 25% of normal density. Published studies of embryonic stem cell implants have shown a 10- to 100-fold variability in cell survival and in graft volume. Pathophysiologic changes at the implant site that compromise cell survival, such as reduced blood flow, increased tissue pH, and abnormal tissue concentrations of ions and neurotransmitters can be monitored **using the MR imaging and spectroscopy methods disclosed by the applicants**, but which are not even addressed in the Major et al. patent. Real time MR imaging at higher Tesla fields, such as disclosed by the applicants, can provide images identifying concentration changes of these introduced and production-stimulated materials, particularly by using RF microcoils in the region where the therapeutic agents are delivered.

It is also well established in the medical literature that stem cells have a propensity to migrate from the site of implant to remote locations. It is also known that stem cell migration is influence by trophic factors and pathophysiologic changes, such as

ischemia. Thus, it is important that the present application provides an *in vivo* dynamic imaging method that can monitor cell migration and eventual in situ localization of implanted stem cells. By comparison, Major et al. disclose only post-mortem histological methods to evaluate cell migration and integration.

The presently claimed technology may be further distinguished from the teachings provided by Major et al. on the basis that certain claims expressly provide for a quantitative assessment of various parameters related to cell viability, as follows:

> "...an imaging means for quantitating the number of cells implanted into a tissue in a human body."
>
> "...an imaging means for quantitating the number of living cells implanted into a tissue in a human body."
>
> "...an MR imaging means for quantitating the number of cell-to-cell membrane contacts in a cell implant in a tissue in a human body."
>
> "...an MR imaging method for quantitatively determining the apparent diffusion coefficient in a population of living cells implanted into a tissue in a human body."
>
> "...an MR method for quantitatively determining the pH and fluid-electrolyte parameters in a population of living cells implanted into a tissue in a human body."
>
> "...an MR method for quantitatively determining the phosphorus and water proton metabolites in a population of living cells implanted into a tissue in a human body."
>
> ...an MR imaging means for quantitating the functional capillary density of the tissue region contiguous with the cell implant.

None of these recitations recited in the claims are taught or even considered by Major et al., alone or in combination with secondary references.

Major et al. do not disclose an imaging means for quantitatively assessing physiologic and metabolic parameters of progenitor or stem cell implants that can non-invasively determine cell viability. The teachings of Major et al. relate to prospective planning of cell implants, as opposed to the claimed technology of a unique methodology of monitoring current operational events and past operational results. Major et al are thus looking at a different time frame than Applicants' claimed technology and are performing different tasks.

The presently claimed technology in this application in particular discloses methods to monitor non-invasively the ongoing viability of the cell implant in terms of whether the cells are adequately perfused by the local microvasculature. The present invention also discloses a method for quantitating the functional capillary density in the anatomic region of the cell implant, for quantitatively determining the metabolic status of a population of living cells implanted into a tissue, and for the MR-assisted visualization of molecular level changes in composition of the cell implant.

Independent Basis of Patentability Because of Quantitating of Cell Viability

Additionally, as recited in certain others of these claims **(Claims 54-58)**, neither the Lemelson or Palti references disclose how metabolic changes in implanted progenitor or stem cells can be quantitatively measured by non-invasive *in vivo* proton spectroscopy with local or volume RF-coils to obtain quantitative proton observable metabolites such as GABA, PCr, creatine, choline, and lactate. The quantitative feature of the present application is important because concentrations of lactate above 2-6 millimolar indicate a significant occurrence of dying or dead cells. Thus, unlike Lemelson and Palti, the present application describes how viable cell implants can be distinguished from dead or dying cells based on quantitative regional indications of lactate to metabolite levels.

The present application also discloses how non-invasive imaging technologies can track, in vivo, C-13 labeled glucose introduced directly into brain tissues together with

the cell implant. Glucose metabolism in the cell implant is assessed by observing the resulting quantitative data from in vivo conversion of the C-13 labeled glucose into C-13 labeled metabolic by-products. The levels and turnover rates of glucose utilization, as measured by the concentrations of the converted compounds, reflect the ongoing viability of the cell implant. Thus, the methods disclosed by the applicants can be distinguished from the Palti patent in which glucose sensitive cells are implanted into tissue to function as surrogate 'glucodetectors' in patients with insulin-dependent diabetes.

Claims 7, 9, 11, 15, 16, 19, 22, 29, 56 and 58 have been rejected under 35 USC 103(a) as unpatenable over Major (as applied against claim 5) when further considered with US Patent No. 5,497,770 (Morcos).

The addition of Morcos to Major et al. does not overcome the deficiencies of Major et al. and in fact provides further distinctions and benefits in the system claimed in the present invention. Although Morcos is attempting to verify cell viability, it is necessary in his procedure to use a **highly invasive** technique which by its very nature may further damage cells. Morcos describes the use of a catheter to "provoke" cells and cause some specific activity which can then be observed or measured as with infrared observation or direct (through the catheter) measurement of ionic effects.

The clear and significant benefits of the present technology can be readily seen. Rather than penetrating the body into the tissue area and provoking tissue, the present system is capable of non-invasive imaging or the use of external imaging using only field coils to provide magnetic field activity (which would not provoke tissue). Morcos uses direct and internal measurement of parameters with a device that must be present in the immediate vicinity of the tissue and must itself create some provocation of the tissue to engender change that can then be observed by internal instrumentality. Coils, even if used in the claimed technology, do not themselves sense or observe, but merely generate

a non-provocative field within which MR observation by the external system can be provided with greater resolution and image strength.

The non-tissue affecting benefits of the present system as compared to that of Morcos should be apparent. There is no motivation to in any way combine the systems of Major et al. and Morcos to provide a system or method such as that described in the claims.

A typical process for Morcos is described as:

> "Once the probe is positioned on the tissue of interest, a baseline measurement is taken. A substrate compound is infused into the tissue as additional measurements are taken. In many instances, it is advantageous to infuse a second substance, a trigger compound, while continuing to take measurements."

As can be seen, this is a highly invasive process wherein materials and apparatus must be locally introduced and local observation performed to provide any evidence of cell viability.

Claims 24 has been rejected under 35 USC 193(a) as unpatentable over Major et al. in view of Chenevert (US Patent No. 6,567,684). Chenevert also fails to overcome and teach the deficiencies of the Major reference. The rejection must fail on at least that ground.

Claims 24 has been rejected under 35 USC 193(a) as unpatentable over Major et al. in view of Dinsmore. Dinsmore also fails to overcome and teach the deficiencies of the Major reference. The rejection must fail on at least that ground.

The rejections under 35 USC 103(a) are clearly in error and must be withdrawn.